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Deposition and Clearance of Inhaled Particles

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Theoretical models of respiratory tract deposition of inhaled particles are compared to experimental studies of deposition patterns in humans and animals, as determined principally by particle size, density, respiratory rate and flow parameters. Various models of inhaled particle deposition make use of convenient approximations of the respiratory tract to predict tractional deposition according to fundamental physical processes of impaction, sedimentation, and difussion. These theoretical models for both total deposition and regional (nasopharyngeal, tracheobronchial, and pulmonary) deposition are compared with experimental studies of inhaled dusts in humans or experimental animals that have been performed in many laboratories over several decades. Reasonable correlation has been obtained between theoretical and experimental studies, but the behavior of very fine (<0.01 μm) particles requires further refinement. Properties of particle shape, charge, and hygroscopicity as well as the degree of respiratory tract pathology also influence deposition patterns and further experimental work is urgently needed in these areas. The influence upon deposition patterns of dynamic alterations in inspiratory flow profiles caused by a variety of breathing patterns also requires further study, and the use of such techniques with selected inhaled particle size holds promise in possible diagnostic aid in diagnosis of normal versus disease conditions. Mechanisms of conducting airway and alveolar clearance processes involving mucociliary clearance, dissolution, transport to systemic circulation, and translocation via regional lymphatic clearance are discussed. The roles of the pulmonary macrophage in airway and alveolar clearance are described, and the applicability of recent solubility models for translocation or deposited materials to liver, skeleton, or other systemic organs is discussed.

Introduction

Man has for thousands of years been generating hazardous aerosols during the mining and smelting of metals in order to make tools and weapons, as well as in the mining and use of fossil fuels (*1*). In the search for metal ores of various types, both acute and long term chronic respiratory diseases have developed and it has become necessary to much more thoroughly understand the patterns and factors involved in the deposition of inhaled airborne hazards (*2,3*). It has become tragically apparent that knowledge of the concentration of an airborne contaminant and the total inhaled air volume alone is not sufficient reliabley to predict the physiological or pathological results of inhalation exposure. Additional information is urgently needed concerning the depth of penetration and fractional removal of inhaled particles to determine their critical sites of action and their related clearance mechanisms. Clarification is also needed of interrelated roles of aerosol parameters such as size, shape, density, hydroscopicity and electric charge as these determine the sites of deposition of particles in the respiratory tract. In addition the physiological parameters that affect dsposition of aerosols need further definition. These may involve lung morphometry in order to define airway diameters, lengths and branching angles, as well as further studies of dynamic respiratory flow profiles, air movement and airway constriction caused by exposure to reactive agents or to other impair-

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ment resulting from chronic respiratory disease. In this discussion the term, "aerosol," refers to any system of solid or liquid particles of sufficiently small diameter to maintain stability as a suspension in air.

The Respiratory Tract

Mathematical or physical models of the deposition of inhaled airborne particles use approximations of the respiratory tract that are represented by straight lengths of tubes of specified diameters and lengths, branching at fixed angles; from these models percentage deposition factors are calculated for various sizes of particles. An inhaled aerosol first encounters a filtering mechanism at the entrance to the nares that will impede large particles and promote their impaction upon the walls of the airways. The air then passes through the posterior nares becoming warm and humidified as it passes over flattened projections (conchae). The complex channels promote deposition of particles on a mucus blanket which flows towards the pharynx. The aerosol may next deposit in the nasopharyngeal region which continues through the oral pharynx to the larynx. Air flow then proceeds through the trachea and separates into the right and left bronchi; these airways separate into the various secondary lobar branches and subsegmental branches, finally devolving into smaller quaternary branches, numbering ≅800. As the branching occurs further into smaller airways, the mucus-producing goblet cells and circulatory glands lining these airways gradually disappear, and the epithelial lining becomes nonciliated at the level of the terminal bronchioles; these are less than 1 mm in diameter. Terminal bronchioles separate into respiratory bronchioles which are nonciliated and number nearly 150,000 (*4*). The respiratory bronchioles, in turn, divide into alveolar ducts which are almost entirely lined with alveoli; there are about 26 million of these ducts, giving rise to roughly 50 to 100 million alveolar sacs. These sacs provide 30 to 100 m^2 of gas exchange surface in human lungs (*5*).

Lymphatic channels are found throughout the pleura and septa, draining into lymph nodes at the hilus of the lungs and into nodes surrounding the trachea. These lymph channels may constitute an important avenue of pulmonary clearance of insoluble deposited particles (*6*). The tracheobronchial lymph nodes may become secondary reservoirs of deposited material.

In the course of normal respiration, rates of air flow entering the respiratory tract range from zero to a maximum of 60-120 l./min in response to the amount of work being performed (*7*). During the period of both inspiration and expiration, processes following physical laws of deposition will take place. The three principal means of deposition are inertial impaction, sedimentation, and diffusion. These mechanisms are greatly influenced by changes in air flow and by differences in residence times that may occur during a cycle of respiration at each level of the respiratory tract. At ventilation rates of 200 ml/sec, air flows may range from 180 cm/sec in the main bronchi to only 1/25,000 cm/sec in the alveolar ducts (*8*).

Mechanisms of Deposition

Impaction: Inertial impaction of inhaled particles tends to be the principal mechanism of large particle deposition in the respiratory tract, acting on particles ranging from a few micrometers to greater than a 100 μm in diameter. The inertia of a large airborne particle will tend to cause it to move in its initial path when the supporting airstream is suddenly deflected by nasal turbinates or branching of airways. The probability of this inertial deposition I appears to be directionally proportional to the terminal settling velocity of the entrained particle V_p times the velocity of the airstream V_a, and inversely proportional to the radius r of the airway:

$$I \propto V_p V_a \sin(\theta/rg)$$

where g is the gravitational constant. Thus, the larger the particle, the higher its settling velocity, the greater the air velocity, the greater the bend angle θ, and the smaller the airway radius, the greater will be the probability of deposition by inertial impaction (*9*).

Sedimentation: Sedimentation or the settling under the force of gravity, is a second very important mechanism for deposition. Every particle that is allowed to fall in air will accelerate to a terminal settling velocity at which the force of gravity is balanced by the resistance of the air through which the particle is falling:

$$V_t = (\sigma - \varrho) g d^2 / 18\,\gamma$$

where γ is the viscosity of air and σ and ϱ are the densities of the particle and air, respectively. As the particle diameter d becomes very small, i.e., of the same order as the mean free path of the molecules, air resistance decreases, and a correction factor (Cunningham) must be applied to de-

scribe this settling motion (*10*). In general, this terminal settling velocity may be given as 2.9×10^5 times the density of the particle times the square of the diameter of the particle, in units of centimeters per second (*11*). This illustrates the governing parameters of particle density and size. Models of respiratory tract deposition are frequently based upon a technique of normalizing employing the "aerodynamic equivalent diameter" which is defined as the diameter of a unit density sphere that has the same terminal settling velocity as the given particle. If the airway containing the particle is at a given angle with the horizontal, then the ratio of distance of fall to maximum distance for deposition is given as the terminal settling velocity times the time of travel times the cosine of the branching angle divided by the diameter of the airway (*9*). Sedimentation is one of the primary mechanisms of deposition of inhaled particles having diameters of 0.1 μm to more than 50 μm.

Diffusion: Deposition by diffusion or Brownian motion in the respiratory tract involves very small particle sizes, particularly those having diameters of tenths to thousandths of a micrometer. These particles are displaced by bombardment due to the random motion of gas molecules in air. The extent of this displacement Λ is inversely proportional to the viscosity of the air γ and to the diameter of the particle d, and is directly proportional to the residence time t of the particle:

$$\Lambda = \left(\frac{RT\,Ct}{N\,3\pi\,\gamma d} \right)$$

where R, T, and N have their usual meaning.

Thus the probability of deposition by diffusion will increase as this displacement motion increases relative to the size of the confining space (*11*). This mechanism of deposition increases with decreasing particle size, whereas deposition by sedimentation decreases with decreasing particle size, and as a result there occurs a minimum deposition at which the displacment velocity by terminal settling is low and the displacement velocity due to diffusion is also low. This occurs with aerodynamic particle diameters of roughly 0.2-0.5 μm (*3*).

The mechanisms described above determine the extent of deposition of inhaled particles but are dependent upon anatomical arrangement of air passages, the rate of air flow into each generation of airway, and the residence time of the particle. Broadly, impaction will affect the largest particles and will take place in the upper regions of the respiratory tract where airflows are high. Deposition by sedimentation will predominate at smaller generations of bronchi or bronchioles, and in the parenchymal lung, having a major influence on deposition of particles down to sizes on the order of <1 μm (assuming unit density), although deposition by diffusion will predominate for particles <0.2 μm. Diffusion is independent of density and affects the smallest particle size ranges, roughly from those of 0.5 μm to less than 0.0002 μm (*12*). This occurs principally in the small airway and gas exchange regions of the lung, but extremely small particles such as condensation nuclei may deposit in larger airways very shortly after entrance into the respiratory tract because of their very high diffusive displacement.

Aerosol Deposition in the Respiratory Tract: Theoretical and Experimental

Total Lung

The first comprehensive theoretical treatment of total respiratory tract deposition was made in 1935 by Findeisen, using a theoretical model composed of a trachea, four generations of bronchi, two generations of bronchioles, alveolar ducts, and sacs, with an airflow of a constant 200 ml/sec at 14 cycles/min (*13*). This model showed impaction to be the primary means of deposition higher in the respiratory tract, while sedimentation appeared to be the major process of deposition in the bronchiolar lung, where inhaled particle deposition is expected to increase with increasing particle density and diameter. Diffusion was calculated to be the prinicipal means of deposition in the respiratory lung. The theoretical curve predicted by Findeisen is illustrated as curve 1 in Figure 1. Landahl in 1950 described a model of the lung including both the mouth and the pharynx with two orders of alveolar ducts, calculating the probabilities for the three mechanisms of praticle deposition and combining these probabilities for each region (*11*). Landahl employed an approximation of the respiratory cycle having 3/8 of the total cycle for inspiration and 3/8 for expiration, again with constant flow rates. Curves 2, 3, and 4 illustrate his theoretical calculations for different tidal volumes and respiration rates. These show a predicted increased deposition with larger tidal volume when comparing curve 3 and curve 2. Comparing curve 3 with curve 4 illustrates that little change is expected in deposition

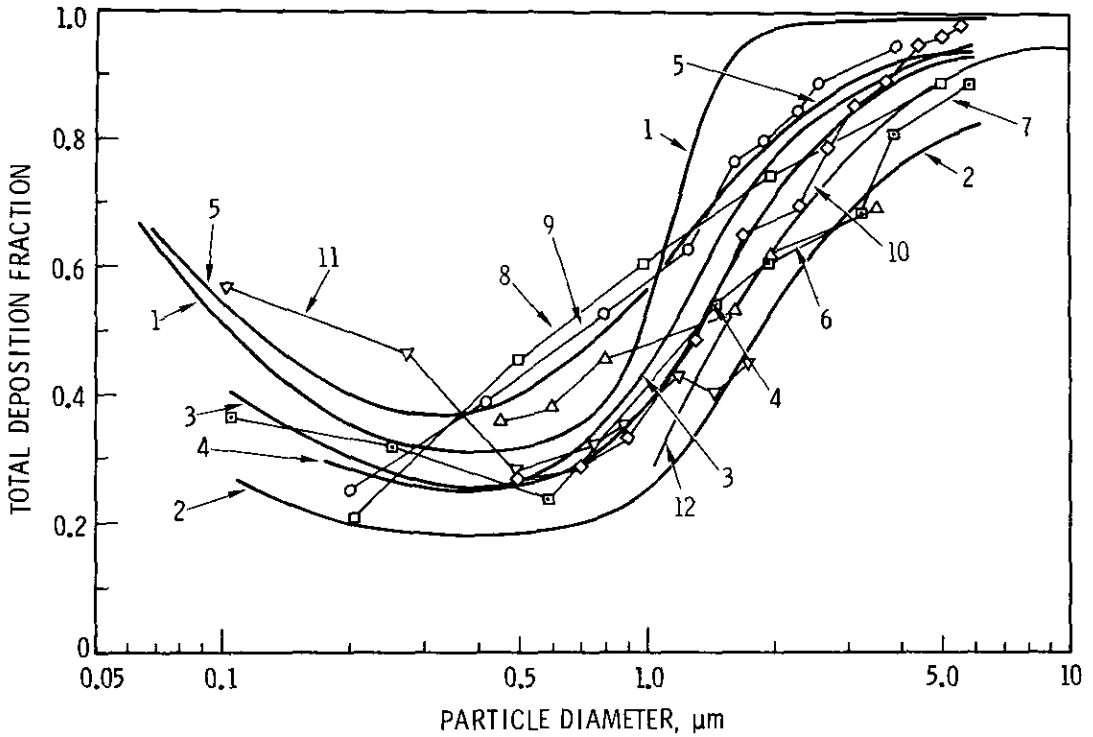

FIGURE 1. Theoretical curves and measured experimental values for total respiratory tract deposition of inhaled particles. Note fairly uniform agreement on minimum deposition at 0.2-0.5 μm: (1) theoretical, Findeisen (*13*), 200 ml/sec, 14 respirations/min; (2) theoretical, Landahl (*11*), 300 ml/sec, 5 respirations/min, tidal volume 450 ml; (3) theoretical, Landahl (*11*), 300 ml/sec, 7.5 respirations/min, tidal volume 900 ml; (4) theoretical, Landahl (*11*), 1000 ml/sec, 15 respirations/min, tidal volume 1500 ml; (5) theoretical, Beeckmans (*16*), 5 respirations/min, tidal volume 1350 ml; (6) experimental, Wilson and LaMer (*33*), 5.5 respirations/min; (7) experimental, Landahl et al. (*9*), 7.5 respirations/min, tidal volume 900 ml; (8) experimental, Gessner et al. (*35*), 15 respirations/min, tidal volume 700 ml; (9) experimental, Van Wijk and Patterson (*32*), 19 respirations/min, tidal volume 700 ml; (10) experimental, Dennis (*17*), 13.3 respirations/min, tidal volume 720 ml; (11) experimental, Dautrebande and Walkenhorst (*18*), 10 respirations/min, tidal volume 990 ml; (12) experimental, compilation by Davies (*19*), 15 respirations/min, tidal volume 600 ml.

fraction by increasing respiration rates. Sinclair and LaMer developed in 1949 a generator that produced monodispersed aerosols, i.e., single-sized aerosols (*14*). This was used in tests with human subjects in which four successive fractions of exhaled air were collected and analyzed at various respiratory rates. The results are shown by curve 7 and illustrate good agreement with the corresponding theoretical curves by Landahl illustrated in curve 3. In 1957, Altschuler et al. (*15*) examined the total and regional deposition of monodispersed aerosols of a density of 1.3 and measured particle concentrations and successive fractions of exhaled air using carbon dioxide levels to calculate respiratory dead space. They found a deposition minimum as predicted at 0.4 μm and found that slow, deep breathing increased deposition as predicted by Landahl's deposition studies. In 1965 Beeckmans (*16*) examined Landahl's model using computer simulations in order to determine the effect of recycled nondeposited aerosols and interpulmonary gas mixing; these data are described by curve 5. Beeckmans' revised model predicted a significant drop in total deposition as tidal volume was decreased; for example, if the tidal volume was reduced from 1600 ml to 400 ml, predicted total deposition dropped from 50% to 20% for 1 μm particles and from 80 to 40% for 0.5 μm particles. Experimental studies were also made by Dennis in 1961 using stearic acid particles, as shown in curve 10 (*17*). He also observed that deposition increased as respiration rates were lowered below 15 cycles/min. However, he did find that deposition was increased, at more than 15 cycles/min, perhaps due to increased impaction with increases in airflows. Curve 11 of Figure 1 shows the results of studies made by Dautreband and Walkenhorst (*18*) on coal dust

deposition, with a minimum deposition of 30% at approximately 0.5 μm. Davies (*19*) has recently derived formulae based on continuity between suspended and deposited aerosol fractions, providing a sound basis for theoretical deposition (curve 12) Heyder et al. (*20*), in studies of the total lung deposition of 0.2-1 μm di-2-ethylhexyl sebacate droplets in humans (tidal volume 500 ml), showed values of 8-14% deposition; the reason for these somewhat lower values has not been fully explained (*20*).

Nasopharyngeal Deposition

Nasopharyngeal deposition was first modeled by Landahl in 1949 using the four volumes representing sections of the upper portion of the respiratory tract (nares to pharynx) (*21*). This study predicted that deposition of the largest of the inhaled particles would occur in this region and that removal by the mechanism of impaction would predominate. The model was found to be in agreement with the experimental dat obtained by passing aerosols through the nose and mouth of experimental subjects using such materials as sodium or potassium bicarbonate, corn oil, glycerol mists, and methylene blue. In 1961 Pattle (*22*) studied nasal depositions of several sizes of monodispersed methylene blue particles obtained using the spinning disk generator. He determined that the fractional nasal penetration of particles could be described as

$$\text{Fractional nasal penetration} = 0.95[1 - 0.5 \log (D^2F/20.2)]$$

where D is the particle diameter and F is the flow (liters/minute). Conversely, nasal deposition for a given particle size was found to be expressed as

$$\text{Nasal deposition} = -0.62 + 0.475 \log D_a^2 F$$

where D_a is the aerodynamic diameter. This predicts that particles of the largest inhalable size (100 μm to about 20 μm) will deposit almost quantitatively in the nose and the nasopharyngeal regions (*23*). Further developments by Houman et al. (*24*) have expressed nasal deposition based on individual mouth vs. nose pressure differences, with a probability of deposition of particles within the nasopharynx equal to

$$\text{Probability} = -1.66 + 0.66 \log D_a^2 F^{1.52}$$

based on the pressure differential between mouth and nose. This pressure differential may be a more logical predictive parameter, because it reflects the interaction of the anatomical cross section with the air flow rather than air flow alone.

The extent of deposition for very small particles within this region (particles less than 0.01 μm in diameter) is poorly known. Houman has compared his experimental results with the theoretical predictions of Landahl and found agreement if he assumed that atmospheric condensation nuclei behaved as if they constituted a uniform aerosol of about 0.01 μm diameter (*25*). He also found good correlation when comparing an iodine vapor deposition in nose and mouth to theoretical models. Nasopharyngeal deposition of both materials increased as the inspiratory airflow decreased, indicating that diffusion is the dominant mechanism for this deposition; at the highest flow rate of 30 l./min, 75-100% of the iodine vapor was deposited in the nose and mouth.

Deposition of larger particles in different locations within the nasopharynx can have a major influence on the relative retention times and associated risks of biological damage from inhaled toxic materials. Lippmann (*26*) has found that 33 to 64% of test monodisperse aerosols of 1.1-4.6 μm diameter were deposited in the nonciliated anterior nares; two subjects still retained 50% of the material deposited in the head at 9 hr after inhalation. Nasopharyngeal deposition studies by Fry and Black (*27*) also show that at least 45% of deposition of 2-10 μm particles occurs in the anterior portions of the nasal airways and may show two phases of biological half-times of less than 20 min and of 3-12 hr; the remaining particles are deposited somewhat deeper in the ciliated nasopharynx, experiencing more uniform clearance to the gastrointestinal tract. These studies indicate that the deposition site within the nasopharyngeal region may be a crucial factor, since mucociliary transport may be very slow in some areas but may be quite rapid in others.

Tracheobronchial Deposition

Experimental studies of tracheobronchial deposition have been conducted in humans primarily using mouth inhalation, bypassing much of the nasopharyngeal area, and more recently using single-sized or monodispersed aerosols having median diameters of 1.3-8 μm (*28*). Extensive studies by Lippmann and Albert using monodispersed iron oxide spheres labeled with radioactive gold, chromium, or technecium in both humans and miniature donkeys have shed light upon deposition and clearance phenomona in this region of the lungs. Regional deposition was

measured from clearance data obtained by external lung and head monitoring using scintillation detectors. These authors have observed large differences in tracheobronchial deposition fractions among individual human subjects. Deposition in this region (for mouth breathing) appears to be largely from impaction, at least for particles greater than 4 μm and of unit density. The calculated deposition fractions for these sizes suggested that deposition should occur by impaction within the first 10-12 airway generations. However a transition then begins to occur with deposition beyond the 12th generation as well as deposition in the bronchiolar region occurring primarily by sedimentation.

In 1966 the Task Group on Lung Dynamics of the International Commission on Radiological Protection made use of the Findeisen model for tracheobronchial deposition, finding that subsequent, more sophisticated, models added very little to the overall accuracy of experimental findings and their correlation with theoretical models (*23*). They used a variety of respiratory frequencies and tidal volumes and computed the deposition due to impaction, sedimentation, and diffusion, finding that the total trancheobronchial deposition seldom exceeded 10% of the inhaled aerosol mass for nose breathing, as shown in Figure 2. The Task Group simplified their deposition estimates by using a single percentage deposition that is 8%. Morrow has pointed out (*29*) that mass deposition of an aerosol is controlled by the larger particles' initial impaction in the bronchial tree; this is particularly important when respiration is by mouth because very few particles greater than 5 μm will penetrate the nose.

Deposition in the tracheobronchial region can be altered by physiological or pathological factors. Lippmann, Albert, and Peterson have conducted studies (*30*) in which it was found that deposition in the tracheobronchial region was greatly enhanced for asthmatic and bronchitic patients, and was also higher than normal in cigarette smokers who inhaled 1-5 μm diameter test particles.

Pulmonary Deposition Patterns

As discussed above, theoretical models have been developed to describe not only total deposition but also regional deposition within the respiratory tract; the latter is more difficult to evaluate experimentally. Theoretical and experimental results for fractional pulmonary deposition of the total inhaled aerosol are shown in Figure 3. Findeisen's theoretical studies are

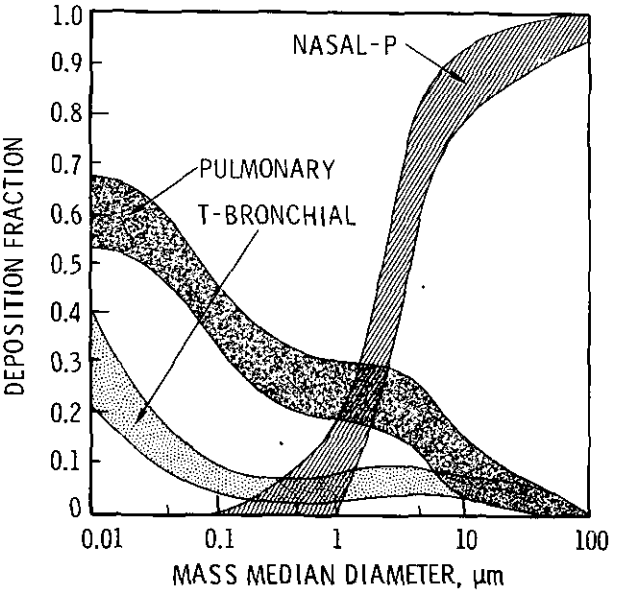

FIGURE 2. Deposition fractions in three regions of the respiratory tract for polydisperse aerosols of specified mass median diameters (aerodynamic). Bands represent curves for particle distribution having geometric standard deviation ranging from 1.2 (almost monodisperse) to 4.5 (very wide range of particle sizes). This figure to describe the gravimetric fraction deposited was developed by the Task Group of Lung Dynamics for the International Commission on Radiological Protection (*21*).

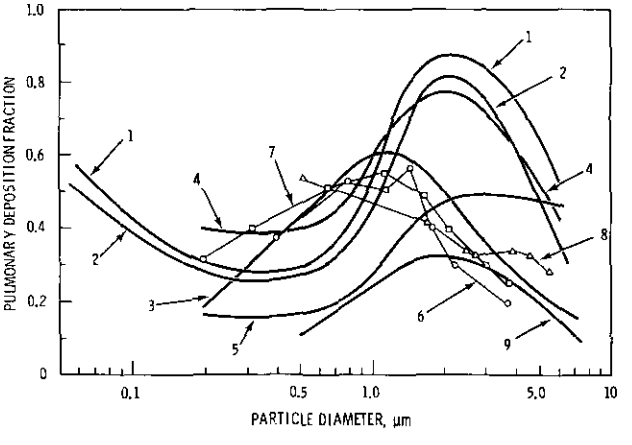

FIGURE 3. Theoretical curves and measured experimental values for pulmonary or alveolar region deposition of inhaled particles: (1) theoretical, Findeisen (*13*), 14 respirations/min, deposition distal to terminal bronchioles; (2) theoretical, Findeisen (*13*), 14 respirations/min, deposition in alveolar ducts and alveoli; (3) theoretical, Hatch and Hemeon (*31*); (4) theoretical, Landahl (*11*), 300 ml/sec, 5 respirations/min, tidal volume 1350 ml, deposition in bronchioles and below; (5) theoretical, Landahl (*11*), 15 respirations/min, tidal volume 450, deposition below terminal broncheoles; (6) experimental, Wilson and LaMer (*33*), 5.5 respirations/min; (7) experimental, Brown et al. (*34*), 15 respirations/min, tidal volume 700 ml; (8) experimental, Gessner et al. (*35*); (9) calculated on the basis of selected experimental data, Davies (*19*), 15 respirations/min, tidal volume 500 ml.

shown in curves 1 and 2. Hatch and Hemeon calculated deposition in the pulmonary region (*31*), based upon studies by Van Wijk and Patterson of inhaled dusts (curve 3) (*32*). Wilson and LaMer in 1948 studied the pulmonary deposition in humans of inhaled monodispersed aerosols of glycerol and water labeled with radioactive sodium chloride (*33*). Respiratory rates were varied from 5.5 to 20 cycles/min, deposition was followed by external monitoring, and exhaled particulates were collected to calculate deposition fractions as shown in curve 6. This curve of experimental findings is very similar to the calculated deposition curve 3 of Hatch and Hemeon (*32*). Brown et al. in 1950/measured pulmonary deposition of aerosols of china clay in humans, keeping minute volumes constant and using respiration rates of 6, 15, and 20 respirations/min (*34*). The results of these studies are shown in curve 7, and agree well with calculated curve 3. In 1949, Gessner et al. studied the deposition of inhaled silica dust (*35*). Their findings, as described by curve 8, show general agreement with theoretical models, i.e., decrease in alveolar deposition of particles larger than 1 μm. Beeckmans in 1965 developed theoretical curves for pulmonary deposition, using Altschuler's concept of intrapulmonary gas mixing (*16*), that were similar to curves 2 and 4. He predicted increases in both total and pulmonary deposition for particles less than 0.1 μm due to diffusion mechanisms. Altschuler et al. recently studied the pulmonary deposition by mouth breathing in humans (*36*), obtaining experimental curves of the expired aerosol concentrations as influenced by expiratory volumes. These were corrected for mechanical aerosol mixing, with the conclusion that the particle size for maximum alveolar deposition is greater than 2 μm in aerodynamic diameter. These authors question the results of Brown's 1950 studies (maximum size for deposition too low) because calculations were based on carbon dioxide levels in expired air, and Altschuler has pointed out (*36*) that aerosol particles do not mix and behave like gas molecules. However Davies (*37*) has examined the size distribution for dusts retained within the lungs, observing size maxima of such distributions by weight to be $\leqslant$ 1.5 μm. Heyder and Davies (*38*) described in 1971 a compartmental model based on tidal reserve and residual air using particle exchange coefficients to predict the deposition of 0.5 μm diameter particles in the lung. They believe that air mixing due to inertial flow and turbulence does not occur anywhere other than in the dead space and that particle exchange is due to the intrinsic motion of the particles. Davies in 1972 determined the fraction of particles in dead space air that deposited in airways during inhalation, and obtained the fraction of inhaled particles that is deposited in the alveolated airways as shown in curve 9 (*19*).

There have been few experimental studies of deposition for particles smaller than 0.1 μm. Hursh and Mercer have studied the deposition of radioactive lead aerosols with activity median aerodynamic diameters of 0.02 and 0.2 μm (*39*). They found 30% total deposition for the larger aerosol and 50-60% deposition for the smaller aerosol. These percentages agree very closely with pulmonary deposition fractions derived by the Task Group on Lung Dynamics (see Fig. 2).

Properties Influencing Deposition of Inhaled Aerosols

As can be seen from the above discussion, the primary properties of inhaled aerosols that govern deposition are those of particle size and particle density. Various heavy materials can be manipulated in terms of particle density by converting to aerodynamic particle size as described above. However there are several factors which additionally influence deposition in selected regions of the respiratory tract. The first of these is shape. It has been found that abnormalities arise in the case of fibrous materials such as asbestos; fibers of length greater than 50 μm have been found deep within the lungs of experimental animals (*40*). In recent studies on the deposition of particles, Beeckmans has concluded that there may be little change due to shape in the proportion of inhaled particles deposited in the lower respiratory tract in the particle size region of maximum pulmonary deposition (*41*). However, the mass of the individual particles in the maximum deposition range tends to increase as particles become more elongated. For example, in terms of spheres, particles of about 2.5 μm are maximally deposited. But for polyelipsoids with an eccentricity factor of 100, the diameter of the sphere of mass equal to these particles for maximum deposition is over 5 μm. This is very important because the mass of such particles is approximately eight times the mass of the maximally deposited spheres. It indicates that the mass median diameter of the deposited particles may be greater in size region of maximum deposition for ellipsoid particles than for spheres.

An additional factor that must be considered is the tendency of certain materials to absorb water (hygroscopicity). This may have a marked effect

on aerosol deposition patterns. As indicated above, Wilson and LaMer have studied pulmonary retention of glycerol particles of several sizes labeled with radioactive sodium chloride (*33*). Their results (curve 6 of Fig. 1) agree well with theory when the particle diameters have been corrected to account for particle growth when equilibrium sizes are reached in the conditions of 99.9% relative humidity in the respiratory tract. Similarly, Dautrebande and Walkenhorst found reasonable agreement with theory for deposition percentages of inhaled sodium chloride *per se* when corrections were made for growth in high humidity (*18*). In general, this effect of hygroscopicity on deposition will be less for particles composed of materials having larger densities and higher molecular weight.

The Task Group on Lung Dynamics has pointed out that particles dispersed into the air by grinding or combustion are electrically charged but that the net charge of these aerosols if slightly aged is usually zero (*23*). Although there may be increased aggregation of these small individually charged particles to cause alterations in particles size distribution by growth, the overall effect of charge itself upon deposition after entering the respiratory tract is probably small. However very small particles that are charged will have higher mobilities and may show increased deposition in the nasopharynx than will be the case for noncharged particles. While it is true that thermal forces are important for particle deposition in the environment, particularly in situations of high thermal gradients such as motor vehicle exhaust or power plant exhausts, thermal gradients in the respiratory tract are low, and a slight rise in the absolute temperature of the particles during inhalation would be expected to have only a minor effect upon their Brownian motion (*23*).

Clearance

Inhaled insoluble particulate contaminants that are deposited in the higher airways lined with ciliated and mucus-secreting cells may be swept into the gastrointestinal tract and may there cause injury directly or may dissolve and cause systemic uptake of the material. Conversely, if the deposited particulate matter is sufficiently soluble, it may have a direct and more rapid transport into the blood stream from the various portions of the lung. It may also move after solubilization via the lymphatic channels either to localize in the regional tracheobronchial lymph nodes or gain entrance into the systemic circulation via continued passage through the lymph. The Task Group on Lung Dynamics in 1966 proposed a model that defined various regions of the respiratory tract for purposes of prediction of deposition and for quantification of subsequent clearance mechanisms (*23*). This model of the respiratory tract describes the nasopharynx as the first major compartment, beginning with the anterior nares extending through the anterior pharynx, the posterior pharynx, and continuing to the level of the larynx. The next compartment is the tracheobronchial region consisting of the trachea and bronchial tree down through and encompassing the terminal bronchioles; this region together with nasopharygeal region constitutes the anatomical dead space of the respiratory tract. In addition, they represent the entire ciliated area of the respiratory tract. The third compartment is the pulmonary region. This compartment consists of several components including the respiratory bronchioles, alveolar ducts, atria and the alveoli themselves; here the epithelium is nonciliated.

The approach of the Task Group was to determine what proportions of inhaled particles will be deposited at each site in the respiratory tract, based primarily on factors of particle size and density. This deposition itself directly influences subsequent clearance patterns in terms of the deposited particles for particular clearance mechanisms associated with differing regions of the respiratory tract. Once these materials are deposited, their physical-chemical characteristics influence their susceptibility to phagocytosis, to become solubilized, or to follow other clearance mechanisms. Two basic methods of particle clearance occur, i.e., endocytosis including phagocytosis, and ciliary movement of mucus. Dust particles being removed by endocytosis show a variety of patterns and half-times of removal apparently dependent upon their number, size, shape, and surface reactivity. An additional method of biological removal involves either the rapid or more prolonged dissolution of the deposited particles, appearing either in the blood stream or the lymph.

The clearance of insoluble dust from nonciliated regions of the respiratory tract that proceed via the mucus-ciliary route appear to occur predominantly following the appearance of the dust within macrophages (*42*). After deposition, dust appears rapidly within these phagocytes. These seem to be able to migrate to airway regions of the lung which contain ciliated epithelium for

movement up larger airways and eventually to the gastrointestinal tract. This endocytosis appears to play an important role in early clearance in the pulmonary region (within the first few hours to several days); however the persistence of dust particles in the lung may also lead to increased cell proliferation and activity. Some experiments report direct penetration between alveolar cells (*43*); this may occur without endocytic activity but the possible mechanism of such penetration remains obscure. Basically, mucus-ciliary transport involves a mechanism whereby either particles directly or particles contained within macrophages may be continuously moved upward into the gastrointestinal tract upon a layer of mucus (*23*). The velocity of the movement of this mucus varies in different regions of the respiratory tract, and may range from fractions of a millimeter in small airways to centimeters per minute in the trachea (*44*). Half-time values from 12 to 30 hr are suggested for this method of clearance (*45*). The Task Group on Lung Dynamics suggested that the physical-chemical factors involving the rate of absorption of a deposited material either through the mucus or through respiratory tract fluids may be the rate limiting process in their clearance (*23*). Dissolved or undissolved components of these materials can interact with protein to produce complexes of a more transportable form. There may be an early appearance of the materials in the liver, skeleton, kidneys, blood or urine, the latter perhaps occurring within a few minutes after exposure (*46,47*). Several experiments indicate the movement of inhaled materials into pulmonary lymphatic channels (*48,49*). There is controversy as to whether this represents a normal or a pathologic response to hazardous materials deposited within the lung. There is little quantitative data on biological half-times of clearnace from the lymphatics.

A number of points made by the Task Group on Lung Dynamics (*23*) concerning these clearance mechanisms per se continue to receive support by more recent findings. Mucus transport mechanisms involving the ciliated epithelium show that many of the aerosols that are deposited on such surfaces will have clearance times on the order of minutes (*50*). Thus even those that are relatively more soluble and dissolve in the mucus will be moved rapidly to the esophagus. In addition, the early recuitable phagocytes together with the ciliary mucus transport will provide a rapid clearance for particles not only in the bronchiolar regions of the respiratory tract but also for a portion of that material deposited in the alveolar lung. A half-time of 24 hr has been suggested for the latter but it may involve several days for transuranium oxides (*51*). Finally there are a number of insoluble dusts that possess a much slower alveolar lung clearance; the kinetics and fractions of clearance in this region appear to depend upon the physical-chemical and toxic properties of the dust particle.

Task Group on Lung Dynamics Model

An interpretation of dust deposition and clearance has been developed by the Task Group on Lung Dynamics as shown in Figure 4 (*23*), Here D-1 is the total amount of dust that is inhaled, D-2 is the fraction that is exhaled, D-3 is the fraction that is deposited in the nasopharyngeal region, D-4 is that fraction deposited in the tracheobronchial region, and D-5 is that deposited in the pulmonary region. Once inhaled dusts are deposited, a fraction of the deposited material will pass either to the blood, to the gastrointestinal tract or to the lymphatic system, depending upon the observed or predicted retentions of the material, i.e., whether it is minimally retained, moderately retained, or avidly retained. Pathway a represents generally a rapid clearance of all types of materials from the nasopharyngeal region to the blood stream; pathway b represents clearance from the same region to the gastrointestinal tract. Similarly, pathways c and d represent clearance of the material deposited in the tracheobronchial region to the blood or to the gastrointestinal tract. The materials deposited in the pulmonary region are cleared by four pathways. Pathways f and g (rapid and prolonged clearance) represent materials actually proceeding to the

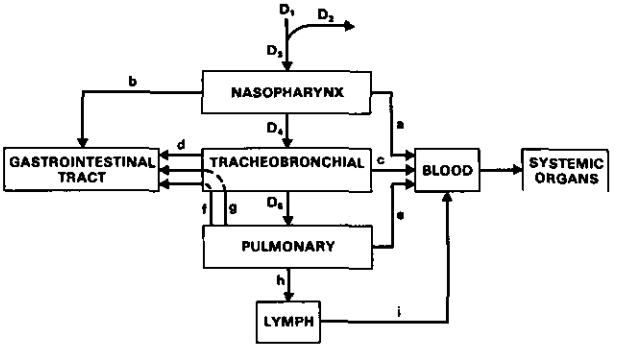

FIGURE 4. Schematic representation of deposition and clearance pathways for inhaled aerosols, derived from the model of the Task Group on Lung Dynamics for the International Commission on Radiological Protection (*21*).

gastrointestinal tract after first being translocated through the tracheobronchial region via the ciliary escalator. Pathway e represents clearance to the blood, pathway h represents clearance via the lymphatic channels, and pathway i represents a movement of at least a portion of the material deposited in regional lymph nodes and associated lymphatics to the blood stream. A table of compounds was constructed (Table 1) in which materials were classified in terms of D, W, and Y, signifying materials cleared with half-times of less than a day (D), materials having half-time clearance of a few days to a few months (W), and half-times of a year or more (Y). Class Y materials are the oxides and hydroxides of most lanthanides and actinides, many of the carbides, and the lanthanides fluorides. Class W indicates moderate retention, encompassing a variety of sulfides and sulfates, carbonates, many phosphates, many of the hydroxides and oxides of periodic table groups 2a, 3a, 4a, 5a, 6a, 8, 2b, 4b, 5, 6, and many of the halides and nitrates. Class D materials have minimal retention, and include many of the nitrates, halides, phosphates, carbonates, sulfates, and sulfides not included in Class W. There are several possible values for both the fractions and the half-times of Class Y materials proceeding by pathway i, i.e., material translocated from lungs through the regional lymph nodes which may eventually reach the systemic circulation (*52,53*).

Table 1. Constants for use with clearance model.[a]

		Class (D)	Class (W)	Class (Y)
Nasopharynx	(a)	0.01/0.50	0.01/0.10	0.01/0.01
	(b)	0.01/0.50	0.4/0.90	0.4/0.99
Tracheobronchial	(c)	0.01/0.95	0.01/0.5	0.01/0.01
	(d)	0.2/0.05	0.2/0.5	0.2/0.99
Pulmonary	(e)	0.5/0.80	50/0.15	500/0.05
	(f)	n.a.	1.0/0.40	1.0/0.40
	(g)	n.a.	50/0.40	500/0.40
	(h)	0.5/0.20	50/0.05	500/0.15
Lymph	(i)	0.5/1.00	50/1.00	1000/0.90

[a] Values taken from the report of the Task Group on Lung Dynamics (*23*), ICRP Publication and amended as in 1968. The first value is the biological half-time in days, the second is the appropriate fraction.

Nasopharyngeal Clearance

The Task Force on Lung Dynamics assumed that rapid transport time would occur for particles deposited in the nasopharynx (*21*). This has not been completely validated, in that while mucus-ciliary movement is very rapid in some areas, there are other areas within this region that are devoid of cilia. Fry and Black found (*27*) that up to 83% of inhaled 5, 7, or 10 μm particles were deposited in portions of the nasal areas that were cleared with biological half-lives of more than 12 hr. It may be necessary to describe clearance times of nearly 24 hr in these regions in the case of some individuals. Studies with nose-only inhalation of radionuclides by large experimental animals at the Inhalation Toxicology Research Institute (*54*) and at the Battelle, Pacific Northwest Laboratories indicate retention times in the nasal turbinates or head on the order of weeks in some cases (*55*).

Tracheobronchial Clearance

Morrow has recently suggested the use of three zones to describe tracheobronchial clearance, i.e., areas up to 10 cm, 10-20 cm, and 20-30 cm from the epiglottis (*29*). His experimental studies with uniform 10 μm polystyrene particles and 7.5 μm mass median diameter iron oxide particles using oral breathing and a multidetection system indicate that half-times of 6, 2.5, and 5 hr were found for the peripheral, intermediate, and higher zones, respectively. Tracheobronchial clearance was thus described by a three-component, six-parameter exponential expression. Morrow, however, points out that mucus velocities do not divide themselves arbitrarily into step gradients, and thus a model was developed to reflect a continuous gradient of rates utilizing the data from many investigations (*56*). Tracheobronchial retention was described as an indirect function of the mass median diameter having a general form of some initial value multiplied by an exponential power of time. This is a power function representation of clearance data. It, too, has shown to be a reasonable approximation of the available data, although there is a wide degree of variability within the reported data itself (*57*). Lippmann and Albert have found (*58*) wide variability between individuals in tracheobronchial clearance rates and fractions, but that cigarette smoking may either decrease or increase rates depending on smoking history. Camner et al. also find (*59*) wide individual variability (6-60 min), but consistency in the same individual in measured clearance rates from repeated studies using ^{18}F-tagged 7μm particles.

Pulmonary Clearance

All of the clearance mechanisms discussed above may affect aerosols deposited within the pulmonary region of the lung. Endocytosis including phagocytosis and pinocytosis readily occurs

in the lung parenchyma. Macrophage removal is accepted to be a major clearance mechanism from this region. Macrophage migration is thought to occur either up the tracheobronchial tree or perhaps via regional lymph nodes. In addition, transported material reaching interstitial sites may move farther and arrive within the lymphatic or blood capillaries, or may be phagocytized by macrophages or histiocytes in these regions. The particles entering lymphatic capillaries may become immobilized upon reaching the lymph nodes, and there serve as secondary reservoirs for gradual input into the systemic circulation (*53*). In addition, particle bearing macrophages may migrate to subpleural and paraseptal positions, to perivascular sites, or to peribronchial positions where long-term storage in the lung may occur, as discussed by Green (*60*). These accumulations may form the sites of origin of several long-term pulmonary diseases. Finally, there are clearance mechanisms related to "solubilization" of particles resulting in material appearing in the lymphatic or blood circulatory systems. The Task Group on Lung Dynamics presents the argument that it is the physical-chemical nature of the materials deposited in this region of the lung that determines the fraction, pathway, and rate of removal, whereas clearance from the tracheobronchial region depends more heavily on biological or physiological controls (*23*); it is not at all certain that this concept applies in cases of developing or established lung pathology.

Mercer has constructed a solubility model which appears to reasonably predict the overall disappearance rates of many deposited materials within the lung (*61*). He assumed that the deposited aerosol was log normal in its particle size distribution and that deposited particles would gradually dissolve and disappear from the lung as a function of the surface area of the particle. The clearance itself is described as a function of three parameters: (1) the median particle size of the mass distribution; (2) a measure of the variability of the distribution, i.e., the geometric standard deviation; (3) the nonequilibrium solubilization of the material as determined over some unit of time. The latter could be obtained by use of a medium and a test material in which the solubilizing medium had properties similar to that of interstitial fluid. Thomas (*62*) has used Mercer's solubility model to estimate the size distribution that must have been deposited in the deep lung of three species (hamster, rat and dog), by following biological clearance in these animals. However, it still remains to be resolved whether such a solubility model can be generally applied to all pulmonary clearance patterns or only to specific cases. The difficulty is that, although the model predicts the clearance half-times of some materials with great accuracy, other mechanisms such as phagocytosis are also very active in removal, particularly for insoluble or toxic materials.

Conclusions

A great deal of intensive theoretical and experimental research during the last few decades has been devoted to the study of deposition of inhaled particles in the respiratory tract, with increasing attention to factors such as size, density, shape, hydroscopicity, and charge that determine deposition in critical regions of either the conducting or gas exchange portions of the lung. These efforts have led to reasonable agreement between results of experimental tests and derived models, allowing prediction of deposition fractions in order to assess risks for many materials over a wide range of particle sizes. However, definitive work is still much needed in the area of deposition of very fine particles such as condensation nuclei that are produced (inter alia) by fossil fuel combustion. Thus, inadequate data exists to evaluate a wide spectrum of air pollution hazards, and this problem is accentuated if such very fine particles (<0.01 μm diameter) serve as carriers for toxic gases or radioactive atoms such as radon or thoron daughters that may selectively irradiate sensitive respiratory epithelial cells, leading to lung cancer or other fatal pulmonary diseases.

The available experimental results concerning clearance fractions and rates for various materials following deposition in different regions of the respiratory tract are continually expanding, but a great deal of additional data is needed to quantify normal clearance pathways, e.g., what factors are involved in activating pulmonary macrophages and to what extent overloading or cytotoxicity by certain materials may markedly alter associated clearance rates or even pathways (mucociliary vs. lymphatic).

There has been a laudatory increase in efforts to measure the effects of various degenerative, proliferative, or infectious disease states upon both deposition and clearance mechanisms. Studies by Palmes et al. (*63*), Lourenco (*64*), and Gamsu et al. (*65*) have shown significant alteration in deposition patterns of inhaled particulates in cases of chronic obstructive pulmonary airway disease. Lourenco found impaired clearance of γ-tagged insoluble aerosols, while Gamsu et al.

observed no significant clearance in up to 15 months from the region of terminal bronchioles and alveloli in cases of chronic obstructive airway disease, using tantalum aerosols. A great deal of additional data will be necessary in order accurately to assess the inhalation hazards of toxic aerosols in the environment to persons with existing pulmonary disorders, and to protect such sensitive individuals from increased risk of induction of diseases such as penumoconiosis, emphysema, or pulmonary carcinoma arising from increased deposition or reduced clearance of such materials from the lungs.

On the other hand, there has been increasing use of suitably tagged aerosols as important aids in the diagnosis of respiratory tract disease. Dry aerosols of ^{99m}Tc-tin(II)-lactose can provide images for lung scintigraphy within 1 min after inhalation (*66*); inhalation scanning with the use of ^{99m}Tc-albumin following perfusion scans with either ^{131}I- or ^{99m}Tc-serum protein macroaggregates has been used to diagnose obstructive airways disease instead of the pulmonary embolism that was originally suspected (*67*).

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